LQTA-QSAR ANALYSIS OF A SET OF ANTIMALARIAL COMPOUNDS

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Introduction: Artemisinin and its derivatives emerged as a new class of antimalarials, which are effective against drug-resistant strains of Plasmodium falciparum. **Objectives**: This study aims the construction of a QSAR 4D model, using recently released package LQTA-QSAR, for a set of 55 artemisinin analogs and its derivatives, including artemisinin as the lead drug, using Partial Least Squares (PLS) regression. **Methodology**: All biological data used in this work were expressed as logarithm of relative activity (logRA). Artemisinin crystal structure retrieved from Cambridge Structural Database, reference code QNGHSU03, was used as starting geometry to build all the ligands. Geometry optimizations of artemisinin and its derivatives were carried out employing MM+ force field, AM1 semi empirical method, *ab initio* HF/3-21G and HF/6-31G methods, and DFT using B3LYP/6-311++G** as basis set. QSARmodeling package was employed to carry out the chemometric analysis. The molecular dynamics simulation protocol for each ligand was the following: 500,000 steps, 0.001 ps (1 fs) at 301K, using GROMACS. All temporal interaction field descriptors (van der Waals and electrostatic energy contributions) were calculated employing the LQTAgrid program using NH3+ as a probe, and considering the conformational ensemble profile (CEP) of each ligand. **Results**: The best QSAR model (N = 43) presented the following statistical parameters values: $q^2 = 0.77$; $r^2 = 0.84$; SEV =0.53; SEC = 0.43 using 3 latent variables and 14 variables. Besides internal validation it was performed prediction on 12 molecules ($q^2_{ext} = 0.67$). The model was tested for its robustness and presence of change correlation by applying y-randomization and leave-N-out (N = 1 to 20) procedures. The interpretation of the descriptors was possible by its graphical representation. **Conclusions**: The presented QSAR model's selected descriptors gave new insights in hotspots for molecular modification in artemisinin analogues, moreover the model is robust and predictive, which, can be useful for design of new potent artemisinin analogues.

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